

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Gary S. Gray, Jerry Carson,
Kashi Javaherian, Paul D. Rennert,
and Sandra Silver.

Group Art Unit: 1642

Examiner: Helms, L

Serial No.: Continuation of 09/227,595

Filed: January 8, 1999

For: CTLA-4-Cy4 Fusion Proteins (As Amended)

Attorney Docket No.: RPN-001CN

Commissioner for Patents
Washington, D.C. 20231

CERTIFICATION UNDER 37 CFR 1.10

Date of Deposit: December 20, 2001

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I hereby certify that this 37 CFR 1.53(b) request and the documents referred to as attached therein are being deposited with the United States Postal Service on the date indicated above in an envelope as "Express Mail Post Office to Addressee" service under 37 CFR 1.10 and addressed to the Commissioner for Patents, Box Patent Application, Washington, D.C. 20231.

Larry Taylor
Name of Person Mailing Paper

Larry Taylor
Signature of Person Mailing Paper

PRELIMINARY AMENDMENT

Dear Sir:

This Preliminary Amendment is being filed concurrently with the continuation application submitted herewith. Prior to substantive examination, please amend the application as follows.

In The Specification:

Please amend the title of the application to read:

--CTLA4-C γ 4 Fusion Proteins--

After the title please insert:

-- Cross Reference to Related Applications

This application is a continuation application of U.S.S.N. 09/227,595. Filed January 8, 1999 (pending), which is a divisional application of U.S.S.N. 08/595,590, filed on February 2, 1996 (pending). The contents of these applications are specifically incorporated herein by reference.--

Please replace pages 52 through 62 of the specification with pages 52 through 72 submitted herewith in Appendix B, which contain the Sequence Listing. New pages 52 through 72 merely add the Sequence Listing in the format required by 37 C.F.R. § 1.812(c).

Please renumber pages 63 through 73, containing the claims and the abstract as originally filed, as pages 73 through 83.

In the Claims:

Please cancel Claims 1-55, 60, 64, 68, 70-91, and amend Claims 56-59, 61, 63, 65-67, and 69 as indicated below (a "version to show changes made" to amended claims is presented in Appendix A). For convenience, all pending claims, whether or not amended, are shown below:

56. (Amended) A modified CTLA4-immunoglobulin fusion protein comprising a first peptide having at least one CTLA4 activity and a second peptide comprising a C γ 4 immunoglobulin constant region which is modified to reduce at least one constant region-mediated biological effector function relative to an unmodified CTLA4-immunoglobulin fusion protein.

57. (Amended) The modified CTLA4-immunoglobulin fusion protein of claim 56, wherein the first peptide comprises an extracellular domain of the CTLA4 protein.
58. (Amended) The modified CTLA4-immunoglobulin fusion protein of claim 57 wherein the first peptide comprises amino acid residues 1-125 of the human CTLA4 protein.
59. (Amended) The modified CTLA4-immunoglobulin fusion protein of claim 56, wherein the immunoglobulin constant region comprises a hinge region, a CH2 domain and a CH3 domain.
61. (Amended) A CTLA4-immunoglobulin fusion protein, comprising a first peptide having at least one CTLA4 activity and a second peptide comprising an immunoglobulin constant region wherein the immunoglobulin constant region comprises the CH1 domain, hinge region, CH2 domain, and CH3 domain from a $\text{C}\gamma 4$ heavy chain.
62. The peptide of claim 61, wherein the immunoglobulin constant region is modified to reduce at least one constant region-mediated biological effector function.
63. (Amended) The peptide of claim 61, wherein the first peptide has at least one CTLA4 activity and the hinge region of the second peptide includes at least one cysteine residue available for disulfide bond formation.
65. (Amended) The CTLA4-immunoglobulin fusion protein of claim 59, wherein the CH2 domain is modified to reduce at least one biological effector function.
66. (Amended) The CTLA4-immunoglobulin fusion protein of claim 65, wherein the biological effector function is selected from the group consisting of complement activation and Fc receptor interaction.
67. (Amended) The CTLA4-immunoglobulin fusion protein of claim 66, wherein the CH2 domain is modified by substitution of an amino acid residue located at a position of an intact immunoglobulin heavy chain selected from the group consisting of position 234, position 235 and position 237.

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69. (Amended) The CTLA4-immunoglobulin fusion protein of claim 67 comprising the amino acid sequence shown in SEQ ID NO: 28.

Please add new Claims 92-94 indicated below:

--92. (New) The CTLA4-immunoglobulin protein of claim 69, wherein said fusion protein comprises a Leu to Glu substitution at position 235 and a Gly to Ala substitution at position 237.

93. (New) The CTLA4-immunoglobulin protein of claim 61, wherein said fusion protein comprises a Leu to Glu substitution at position 235 and a Gly to Ala substitution at position 237.

94. (New) The CTLA4-immunoglobulin protein of claim 67, wherein said fusion protein comprises a Leu to Glu substitution at position 235 and a Gly to Ala substitution at position 237.--

REMARKS

Claims 56-59, 61-63, 65-67, 69, and 92-94 are currently pending in the application. A Sequence Listing which complies with the requirements of 37 C.F.R. §1.821 is submitted herewith. The paper copy of the Sequence Listing is identical in substance to the material on this diskette previously submitted for the parent application 09/227,595. The computer readable form of the Sequence Listing previously submitted for the parent application 09/227,595 is understood to comply with the requirements of §1.824(d).

The Pending Claims are Enabled

It is Applicants position that the quantity of experimentation necessary to practice the claimed invention is not undue and that the experimentation amounts to no more than routine screening.

The Court of Appeals for the Federal Circuit in *In re Wands*, USPQ 2d 1400 (Fed. Cir. 1988) set forth the factors that should be considered when determining whether or not a required amount of

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experimentation is undo as: “(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.” It is Applicants position that under these guidelines, only routine experimentation is required to test the modified fusion proteins of the invention.

The quantity of experimentation to test for reduction in effector function in a particular modified CTLA4 fusion protein is minimal. When determining the quantity of experimentation necessary, the focus is not on the amount of experimentation the entire genus claimed, but rather the amount of experimentation required to practice any particular species of the genus. The Wands court recognized that it would require an infinite amount of experimentation to obtain every single IgM antibody that could be generated with the recited affinity. Therefore, the court focused on the amount of experimentation necessary to make any single IgM antibody with the recited characteristics, and not on the entire genus of antibodies encompassed by the claims.

Applicants provide sufficient guidance and direction to practice the invention across its breadth. In addition to the specific examples of modifications taught by Applicants, Applicants teach several methods by which reductions in constant region effector function can be achieved, e.g., by substitution, addition, or deletion of amino acids as well as exemplary means of performing such modifications. Applicants also teach the regions of the constant region that are important in mediating Fc receptor binding or complement activation (see e.g., page 11, line 18 to page 13, line 18). Screening assays, which can be used to test the effectiveness of modifications, are also provided. For example, at page 45, Applicants teach an assay for measuring Fc receptor binding using the human cell line U937. A lytic assay for the measurement of complement activation is also taught, e.g., at pages 46 and 47. Applicants further teach assays which can be used to demonstrate that any modifications made to the constant region do not interfere with the ability of a modified fusion protein to modulate costimulation, e.g., the T cell proliferation assay taught on page 47.

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In Example 1, Applicants also provide working examples of the construction of a mutated CTLA4Ig fusion protein. In that example, amino acids at immunoglobulin positions 235 and 237 were changed from Leu to Glu and Gly to Ala, respectively, within the IgC γ 4 CH2 domain to eliminate Fc receptor binding. Thus, it appears that the Examiner has focused on modifications to the subject fusion proteins which are described in Applicants working example, rather than considering Applicants' teaching as a whole in determining whether the pending claims are enabled by the specification.

It is further Applicants position that the state of the art required to practice the claimed invention is high and that the nature of the invention is such that, given the teachings of the specification and the knowledge of one of the art, the ordinarily skilled artisan would readily be able to make amino acid substitutions to CTLA4Ig fusion proteins as claimed.

Applicants further assert that the level of predictability in the art is high. This is so because although one may not be able to predict a priori which modified fusion protein will have reduced effector function, the testing of such molecules for reduction in effector function requires no more than routine screening. The Wands court stated that "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." It is Applicants position that the screening of modified forms of CTLA4 (made as taught by Applicants or made using other methods known in the art) for reduction of constant region mediated effector functions constitutes no more than routine experimentation and is not undue.

With respect to the breadth of the claims, Applicants note that it is only the C γ 4 immunoglobulin constant region, which is modified to reduce at least one constant region-mediated biological effector function. Applicants further note that Claim 65 further requires that the modification be in the CH2 domain. Claims 67, 92, 93, and 94 recite specific substitutions, which

are to be made. Claim 69 requires that the modified fusion protein comprise a specific amino acid sequence.

Thus, the instant specification provides sufficient guidance to support the full breadth of the invention as claimed.

Rejection of Claims 56-59, 65-67, and 92, and 94 Under 35 USC 103(a)

In the parent application serial no. 09/227,595, Claims 56-59, 65-67, 92 and 94 were rejected under 35 USC 103(a) as being unpatentable over Linsley et al. (US Patent 5,434,131, issued 7/18/95) and further in view of Lund et al. (*J. of Immunol.* 147:2657-2662, 1991) and Canfield et al. (*J. Exp. Med.* 173:1483-1491, 1991) and Strom et al. (US Patent 5,958,403, filed 7/11/94). More specifically the Examiner stated:

Strom et al. teaches CTLA4Ig fusion proteins with the immunoglobulin Fc region (see page 9 of response). Strom also provides reasons why it is important to modify the Fc region to alter biological effector functions and from Canfield and Lund one skilled in the art would realize what regions and residues to alter for reducing effector functions. ... Thus, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

To establish a *prima facie* case of obviousness for the claimed invention, there must have been some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings in the manner proposed by the Examiner. Second, there must have been a reasonable expectation of success at the time the invention was made. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The prior art must suggest "to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process" and "[b]oth the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Dow Chemical Co.* 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988).

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The Examiner relies on the disclosure of Strom et al. as teaching "CTLA4 Ig fusions wherein the Fc portion does not activate complement," and as providing motivation for one of skill in the art to make additional modifications to a CTLA4Ig fusion protein.

This rejection is respectfully traversed. Applicants' invention predates the filing date of the Strom et al. patent. An executed Declaration under 37 CFR §1.131 by inventors Gary S. Gray, Jerry Carson, Kashi Javaherian, Paul D. Rennert, and Sandra Silver, which antedates the filing date of the Strom et al. patent is enclosed. The Declaration is supported by evidence presented in Appendix A of the Declaration. In the Declaration, the inventors state that the date of invention was prior to July 11, 1994, the filing date of the Strom et al. patent. Applicants further note that the application to which the Strom et al. Patent claims priority, USSN 08/024,569, fails to teach or suggest any modifications to CTLA4Ig fusion proteins, let alone the modifications presently claimed. It is respectfully submitted that in light of this Declaration, the Strom et al. patent does not qualify as prior art under 35 USC §102(e). The pending claims would not have been obvious in view of the remaining references cited in the parent application, e.g., the disclosures of Linsley et al., Lund et al. and Canfield et al., since those disclosures neither teach nor suggest all of the limitations of the claims, MPEP 2143.

In view of the foregoing, Applicants respectfully request withdrawal of this rejection.

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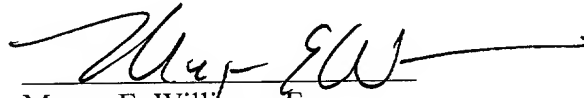
SUMMARY

In view of the foregoing remarks, consideration of the subject application and allowance of all pending claims is respectfully requested.

If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the examiner is urged to call Applicants' Attorney at (617) 227-7400.

Respectfully submitted,

LAHIVE & COCKFIELD, LLP



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APPENDIX A

Version to show changes made to Claims 56-59, 61, 63, 65-67, and 69:

56. (Amended) A modified CTLA4-immunoglobulin fusion protein comprising a first peptide having at least one [a] CTLA4 activity and a second peptide comprising a C γ 4 [an] immunoglobulin constant region which is modified to reduce at least one constant region-mediated biological effector function relative to an unmodified CTLA4-immunoglobulin [a CTLA4-IgG1] fusion protein.

57. (Amended) The modified [A] CTLA4-immunoglobulin fusion protein of claim 56, wherein the first peptide comprises an extracellular domain of the CTLA4 protein.

58. (Amended) The modified [A] CTLA4-immunoglobulin fusion protein of claim 57, wherein the first peptide comprises amino acid residues 1-125 of the human CTLA4 protein.

59. (Amended) The modified [A] CTLA4-immunoglobulin fusion protein of claim 56, wherein the immunoglobulin constant region comprises a hinge region, a CH2 domain and a CH3 domain.

61. (Amended) A CTLA4-immunoglobulin fusion protein, comprising a first peptide having at least one [a] CTLA4 activity and a second peptide comprising an immunoglobulin constant region wherein the immunoglobulin constant region comprises the [a heavy chain] CH1 domain, [a] hinge region, [a] CH2 domain, and [a] CH3 domain from a C γ 4 heavy chain.

63. (Amended) The peptide of claim 61, wherein the first peptide having a CTLA4 activity and the hinge region of the second peptide includes at least one cysteine residue available for disulfide bond formation.

65. (Amended) The [A] CTLA4-immunoglobulin fusion protein of claim 59, wherein the CH2 domain is modified to reduce at least one biological effector function [functions].

66. (Amended) The [A] CTLA4-immunoglobulin fusion protein of claim 65, wherein the biological effector function is selected from the group consisting of [complement activation, Fc receptor interaction, and] complement activation and Fc receptor interaction.

67. (Amended) The [A] CTLA4-immunoglobulin fusion protein of claim 66, wherein the CH2 domain is modified by substitution of an amino acid residue located at a position of an intact immunoglobulin heavy chain selected from the group consisting of position 234, position 235 and position 237.

69. (Amended) The [A] CTLA4-immunoglobulin fusion protein of claim 67 [68] comprising the [an] amino acid sequence shown in SEQ ID NO: 28.

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